Internal and Emergency Medicine (2019) 14:1101–1112
https://doi.org/10.1007/s11739-019-02077-5

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Vena cava filters in patients presenting with major bleeding during anticoagulation for venous thromboembolism

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Received: 7 December 2018 / Accepted: 20 March 2019 / Published online: 3 May 2019

Abstract
The association between inferior vena cava filter (IVC) use and outcome in patients presenting with major bleeding during anticoagulation for venous thromboembolism (VTE) has not been thoroughly investigated. We used the RIETE registry to compare the 30-day outcomes (death, major re-bleeding or VTE recurrences) in VTE patients who bled during the first 3 months of therapy, regarding the insertion of an IVC filter. A propensity score matched (PSM) analysis was performed to adjust for potential confounders. From January 2001 to September 2016, 1065 VTE patients had major bleeding during the first 3 months of anticoagulation (gastrointestinal 370; intracranial 124). Of these, 122 patients (11%) received an IVC filter. Patients receiving a filter restarted anticoagulation later (median, 4 vs. 2 days) and at lower doses (95 ± 52 IU/kg/day vs. 104 ± 55 of low-molecular-weight heparin) than those not receiving a filter. During the first 30 days after bleeding (after excluding 246 patients who died within the first 24 h), 283 patients (27%) died, 63 (5.9%) had non-fatal re-bleeding and 19 (1.8%) had recurrent pulmonary embolism (PE). In PSM analysis, patients receiving an IVC filter ($n = 122$) had a lower risk for all-cause death (HR 0.49; 95% CI 0.31–0.77) or fatal bleeding (HR 0.16; 95% CI 0.07–0.49) and a similar risk for re-bleeding (HR 0.55; 95% CI 0.23–1.40) or PE recurrences (HR 1.57; 95% CI 0.38–6.36) than those not receiving a filter ($n = 429$). In VTE patients experiencing major bleeding during the first 3 months, use of an IVC filter was associated with reduced mortality rates.
Clinical Trial Registration NCT02832245.

Keywords Anticoagulants · Bleeding · Vena cava filter · Mortality · Venous thromboembolism.

Introduction

Bleeding is the most feared complication in patients receiving anticoagulant therapy for venous thromboembolism (VTE). In the literature, the rate of fatal bleeding in VTE patients receiving anticoagulant therapy ranged around 0.5–1.0 deaths per 100 patient-years [1–3] Current management of patients with major bleeding usually starts with immediate discontinuation of anticoagulant therapy, followed by an intervention (endoscopy, coiling, surgery) and treatment with blood transfusion, vitamin K, prothrombin complex concentrate, fresh frozen plasma, or insertion of a vena cava filter (IVC), based on the type and severity of the bleeding and local protocols and resources [4–9]. IVC filters have been available as a preventive option for patients at risk for pulmonary embolism (PE) since the 1970s and are widely used as a therapeutic option in patients with VTE or to prevent PE without current VTE [10]. In a prior study, VTE patients at high risk for bleeding receiving an IVC filter had a lower risk for recurrent PE and PE-related death within the first 30 days than those who did not [11]. In a subsequent study, the use of a filter was also associated with lower mortality at 30 days in patients presenting with PE recurrences during anticoagulant therapy [12]. However, the association between use of IVC filters and outcomes in patients presenting with major bleeding during the course of anticoagulation for VTE has not been thoroughly evaluated.

A full list of RIETE investigators is given in the acknowledgements.

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The Registro Informatizado de Enfermedad Trombo Embólica (RIETE) is a multicenter, ongoing, international registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245) [11, 13–15]. Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment and outcomes in patients diagnosed with VTE [11, 13–16]. In the current study, we aimed to assess the association between the use of IVC filter insertion and all-cause mortality within the first 30 days in patients presenting with major bleeding during the first 3 months of anticoagulant therapy for VTE.

Methods

Patients and data source

Consecutive patients with acute deep vein thrombosis (DVT) or PE confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT scan, ventilation–perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. The methodology of the registry has been described elsewhere [17].

Inclusion and exclusion criteria

This study screened patients with symptomatic VTE enrolled in RIETE from January 2001 through September 2016 who presented with a major bleeding event during the

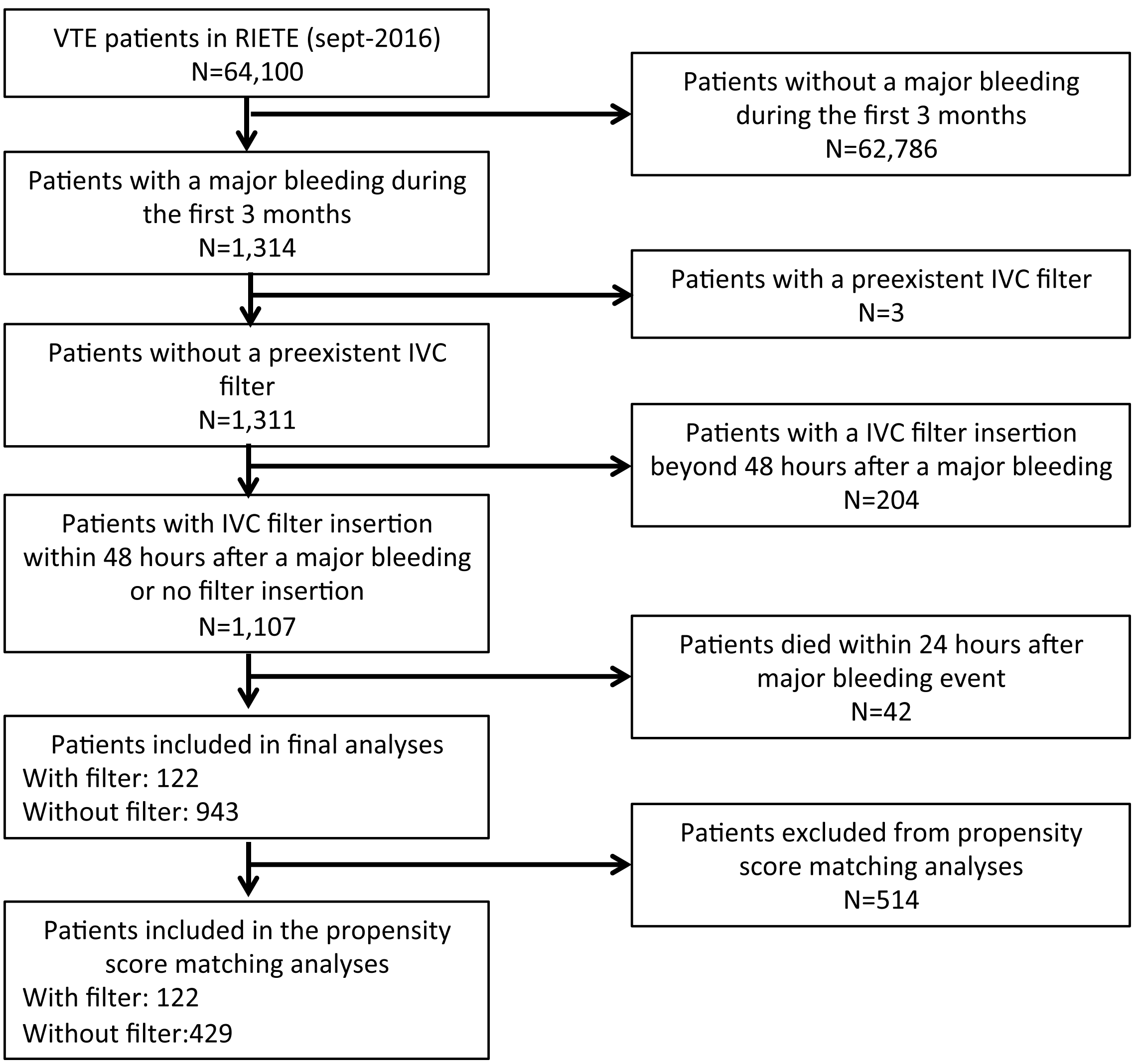

Fig. 1 Flowchart of the patients

first 3 months of anticoagulant therapy. We excluded patients with a pre-existing IVC filter, those undergoing IVC filter placement beyond the first 48 h after major bleeding and those who were not receiving anticoagulant therapy when the index bleeding event prior to inclusion occurred. Bleeding events were classified as 'major' if they were overt and required transfusion of two units or more of blood, or were retroperitoneal, spinal or intracranial, or when they were fatal [9, 18, 19].

To avoid immortal time bias, the current study also excluded those patients who died within 24 h after major bleeding [5]. All patients (or their legal power of attorney) provided written or oral informed consent for participation

Table 1 Clinical characteristics of 1065 VTE patients presenting with major bleeding during the first 3 months of anticoagulation, according to use of vena cava filter

	Vena cava filter	No vena cava filter	Odds ratio (95%CI)	*p*
Patients, n	122	943		
Hospital size > 500 beds,	84 (69%)	544 (58%)	1.62 (1.08–2.43)	0.02
Year of VTE diagnosis,				
2001–2008 vs. 2009–2016	56 (46%)	237 (55%)	0.69 (0.46–1.03)	0.07
Country of origin				
Spain	97 (80%)	778 (83%)	0.82 (0.51–1.32)	0.42
Clinical characteristics				
Male gender	51 (42%)	407 (43%)	0.95 (0.65–1.39)	0.78
Age (mean years ± SD)	69 ± 15	72 ± 15	–	0.02
Body weight (kg ± SD)	75 ± 16	71 ± 14	–	0.005
Initial VTE presentation				
Pulmonary embolism	76 (62%)	568 (60%)	1.09 (0.74–1.61)	0.66
Time from VTE to bleeding				
Mean days (± SD)	10 ± 13	25 ± 24		< 0.001
Day 0 to Day 30	115 (94%)	650 (69%)	7.41 (3.42–16.1)	< 0.001
Current therapy at bleeding				
Low-molecular-weight heparin	89 (73%)	576 (61%)	1.72 (1.13–3.76)	0.01
Unfractionated heparin	15 (12%)	60 (6.4%)	2.06 (1.13–3.76)	0.02
Thrombolytics	2 (1.6%)	15 (1.6%)	1.03 (0.23–4.56)	0.97
Fondaparinux	0	13 (1.4%)	–	0.19
Direct oral anticoagulants	0	14 (1.5%)	–	0.18
Vitamin K antagonists	11 (9.0%)	223 (24%)	0.32 (0.17–0.61)	< 0.001
Site of major bleeding				
Gastrointestinal	34 (28%)	336 (36%)	0.70 (0.46–1.06)	0.09
Haematoma	27 (22%)	228 (24%)	0.89 (0.57–1.40)	0.62
Intracranial	21 (17%)	103 (11%)	1.70 (1.02–2.83)	0.04
Retroperitoneal	15 (12%)	69 (7.3%)	1.78 (0.98–3.21)	0.06
Genitourinary	6 (4.9%)	78 (8.3%)	0.57 (0.25–1.35)	0.20
Other	19 (16%)	129 (14%)	1.16 (0.69–1.97)	0.57
Risk factors for VTE				
Surgery	21 (17%)	118 (13%)	1.45 (0.88–2.42)	0.15
Immobility ≥ 4 days	44 (36%)	309 (33%)	1.16 (0.78–1.72)	0.47
Active cancer	34 (28%)	322 (34%)	0.75 (0.49–1.13)	0.17
Estrogen use	5 (4.1%)	26 (2.8%)	1.51 (0.57–4.00)	0.41
None of the above (unprovoked)	44 (36%)	296 (32%)	1.21 (0.82–1.80)	0.34
Prior VTE	9 (7.4%)	114 (12%)	0.58 (0.29–1.17)	0.13
Underlying conditions				
Chronic lung disease	19 (16%)	139 (15%)	1.07 (0.63–1.80)	0.81
Chronic heart failure	12 (9.8%)	112 (12%)	0.81 (0.43–1.52)	0.51
Anemia	67 (55%)	550 (58%)	0.87 (0.59–1.27)	0.47
CrCl levels < 30 mL/min	14 (12%)	154 (16%)	0.66 (0.37–1.19)	0.17

VTE venous thromboembolism, *SD* standard deviation, *LMWH* low-molecular-weight heparin, *CrCl* creatinine clearance, *CI* confidence intervals in the registry, in accordance with local ethics committee requirements.

Outcomes

The primary outcome was all-cause death within the first 30 days after major bleeding. Secondary outcomes were fatal bleeding, non-fatal major re-bleeding, PE recurrences and DVT recurrences within the first 30 days after bleeding. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Bleeding events were classified as 'major' if they were overt and required transfusion of two units or more of blood, or were retroperitoneal, spinal or intracranial, or when they were fatal.

Baseline variables

Patients enrolled in RIETE had data collected from around the time of index VTE diagnosis that included but were not limited to: demographics; body weight; presence of coexisting conditions such as chronic heart or lung disease; risk factors for VTE including active cancer (newly diagnosed or under treatment [i.e., surgery, chemotherapy, radiotherapy, hormonal or support therapy]), recent immobility (bed rest with bathroom privileges for ≥ 4 days in the 2 months prior to VTE diagnosis), surgery (major surgery within the 2 months prior to VTE); results at hospital admission that included hemoglobin, platelet count and serum creatinine levels. RIETE also collected treatment data that included anticoagulant use (drugs, doses and duration) and vena cava filter use.

Statistical analysis

Continuous variables were reported as mean and standard error (or non-parametric counterparts where needed) and categorical variables were reported as frequency counts and percentages. Hazard ratios (HR) with 95% confidence intervals (CI), as well as *p* values (Mann–Whitney test or *t* test for continuous variables and Cochran–Mantel–Haenszel tests for categorical variables) were presented for each variable analyzed. All outcomes were analyzed in the overall follow-up period (first 30 days). Univariable analysis was conducted yielding odds ratios with 95% CI, as well as *p* values (Cochran–Mantel–Haenszel tests) for each outcome.

Table 2 Thirty-day mortality according to management of bleeding

	Dead	Alive	Odds ratio (95% CI)	*p* value
With vena cava filter, *n*	17	105		
Restart of anticoagulation, *n*	6 (35%)	89 (85%)	0.10 (0.03–0.30)	< 0.001
Time elapsed from bleeding to restart				
Mean days (± SD)	3.7 ± 6.2	25 ± 120	–	0.67
Median days (IQR)	1.5 (0–3)	4 (1–17)		
Low-molecular-weight heparin	5 (29%)	73 (70%)	0.18 (0.06–0.56)	0.001
Mean LMWH daily dose (IU/kg/day)	105 ± 43	91 ± 58	–	0.46
Unfractionated heparin	0	8 (7.6%)	–	0.24
Direct oral anticoagulants	0	0	–	–
Vitamin K antagonists	0	6 (5.7%)	–	0.31
Other	1 (5.9%)	2 (1.9%)	3.22 (0.28–37.6)	0.42
Without vena cava filter, *n*	266	677		
Restart of anticoagulation, *n*	88 (33%)	518 (77%)	0.15 (0.11–0.21)	< 0.001
Time elapsed from bleeding to restart				
Mean days (± SD)	2.3 ± 3.2	12 ± 65	–	< 0.001
Median days (IQR)	1 (0–3)	3 (1–8)		
Median days (IQR)	1.0 (3.0)	3.0 (7.0)	–	0.001
Low-molecular-weight heparin	69 (26%)	401 (59%)	0.24 (0.18–0.33)	0.001
Mean LMWH daily dose (IU/kg/day)	101 ± 59	108 ± 56	–	0.31
Unfractionated heparin	8 (3.0%)	36 (5.3%)	0.55 (0.25–1.20)	0.13
Fondaparinux	0	5 (0.7%)	–	0.16
Direct oral anticoagulants	1 (0.4%)	8 (1.2%)	0.32 (0.04–2.54)	0.25
Vitamin K antagonists	6 (2.3%)	57 (8.4%)	0.25 (0.11–0.59)	0.001
Other	4 (1.5%)	11 (1.6%)	0.92 (0.29–2.93)	0.99

SD standard deviation, *IQR* interquartile range, *LMWH* low-molecular-weight heparin, *CI* confidence intervals

We used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving a cava vein filter. We used logistic regression to estimate propensity scores. We modeled the receipt of a filter using baseline demographic and clinical variables on the basis of their associations with any adverse events after major bleeding. The following covariates were considered in the calculation of the propensity score: size of the hospital (more vs. less than 500 beds); country (Spain vs. other countries); time (patients included from 2001 to 2008 vs. those recruited from 2009 to 2017); risk factors for VTE that included active cancer, metastatic cancer, prior surgery or recent immobility; initial VTE presentation (PE vs. DVT); site of bleeding; elapsed time from the index VTE to the major bleeding event; clinical signs at VTE diagnosis, including heart rate, systolic blood pressure levels, anemia (defined as hemoglobin levels < 13 g/dL in men or Hb < 12 g/dL in women), [20] and creatinine clearance (CrCl) levels at baseline. The nearest neighbor (NN) method was used, with a ratio of 4:1 for vena cava filter. After generation of the propensity scores, we sought to estimate the difference in 30-day outcomes attributable to the

Table 3 Thirty-day outcome according to site of bleeding

	n	Vena cava filter	No vena cava filter	Odds ratio (95% CI)	*p* value
All patients, *n*	1065	122	943		
Death	283 (27%)	17 (14%)	266 (28%)	0.41 (0.24–0.70)	< 0.001
Causes of death					
Bleeding	129 (12%)	3 (2.5%)	126 (13%)	0.16 (0.05–0.52)	0.001
Pulmonary embolism	14 (1.3%)	0	14 (1.5%)	–	0.18
Disseminated cancer	45 (4.2%)	3 (2.5%)	42 (4.4%)	0.54 (0.13–1.59)	0.54
Infection	17 (1.6%)	0	17 (1.8%)	–	0.12
Respiratory insufficiency	16 (1.5%)	3 (2.5%)	13 (1.4%)	1.80 (0.41–5.99)	0.37
Heart failure	8 (0.8%)	1 (0.8%)	7 (0.7%)	1.10 (0.05–7.23)	0.85
Major re-bleeding	63 (5.9%)	5 (4.1%)	58 (6.2%)	0.65 (0.26–1.66)	0.37
Recurrent PE	19 (1.8%)	3 (2.5%)	16 (1.7%)	1.46 (0.42–5.09)	0.55
Recurrent DVT	21 (2.0%)	6 (4.9%)	15 (1.6%)	3.20 (1.22–8.41)	0.01
Gastrointestinal	370	34	336		
Any death	124 (34%)	8 (24%)	116 (35%)	0.58 (0.26–1.33)	0.20
Fatal bleeding	56 (15%)	2 (5.9%)	54 (16%)	0.33 (0.08–1.40)	0.11
Major re-bleeding	28 (7.6%)	2 (5.9%)	26 (7.7%)	0.75 (0.17–3.29)	0.70
Haematoma	255	27	228		
Any death	39 (15%)	4 (15%)	35 (15%)	0.96 (0.31–2.94)	0.94
Fatal bleeding	14 (5.5%)	0	14 (6.1%)	–	0.19
Major re-bleeding	11 (4.3%)	1 (3.7%)	10 (4.4%)	0.84 (0.10–6.82)	0.87
Intracranial	124	21	103		
Any death	43 (35%)	1 (4.8%)	42 (41%)	0.07 (0.01–0.56)	0.002
Fatal bleeding	30 (24%)	1 (4.8%)	29 (28%)	0.13 (0.02–0.99)	0.02
Major re-bleeding	6 (4.8%)	0	6 (5.8%)	–	0.26
Retroperitoneal	84	15	69		
Any death	17 (20%)	0	17 (25%)	–	0.03
Fatal bleeding	12 (14%)	0	12 (17%)	–	0.08
Major re-bleeding	3 (3.6%)	1 (6.7%)	2 (2.9%)	2.39 (0.20–28.2)	0.48
Genitourinary	84	6	78		
Any death	28 (33%)	1 (17%)	27 (35%)	0.38 (0.04–3.40)	0.37
Fatal bleeding	7 (8.3%)	0	7 (9.0%)	.	0.44
Major re-bleeding	5 (6.0%)	0	5 (6.4%)	–	0.52
Other sites	148	19	129		
Any death	32 (22%)	3 (16%)	29 (23%)	0.65 (0.18–2.37)	0.51
Fatal bleeding	10 (6.8%)	0	10 (7.8%)	–	0.21
Major re-bleeding	10 (6.8%)	1 (5.3%)	9 (7.0%)	0.74 (0.09–6.20)	0.78

PE pulmonary embolism, *DVT* deep vein thrombosis, *CI* confidence intervals insertion of a filter using a greedy matched-pair analysis that has a 4:1 matching algorithm and does not allow for replacements. We randomly selected a patient in the filter subgroup and then matched that patient with the nearest patient in the non-filter subgroup within a fixed caliper width of 0.10 of standard deviation of propensity score [21]. To assess the success of the matching procedure, we measured standardized differences of means (SDM) in percentage points in observed confounders between the matched groups [22]. A SDM lower than 10% was considered as a good matching but if it was higher than that, the imbalanced covariate was included in the final post-matching multivariable analysis. We used psmatching3 extension bundle for the propensity score analyses with SPSS software (version 20, SPSS Inc., Chicago, Illinois).

Results

In the study period, from a total of 67,195 consecutive patients with VTE, 1314 (1.96%) developed major bleeding within the first 3 months of anticoagulant therapy. Of these, 246 (19%) died within the first 24 h after bleeding and 3 had an IVC filter already inserted at baseline. These patients were not included in the study. Thus, the study included 1065 patients with acute VTE who bled during the first 3 months of anticoagulant therapy: 644 initially presenting with PE (with or without concomitant DVT) and 421 presenting with DVT alone (Fig. 1). The most common sites of major bleeding were the gastrointestinal tract ($n=370$), hematoma ($n=255$), intracranial ($n=124$), retroperitoneal ($n=84$) and genitourinary ($n=84$). In all, 122 patients (11%) received an IVC filter.

Patients receiving an IVC filter were younger, weighed more than those not receiving a filter and were more likely to be hospitalized in hospitals with over 500 beds (Table 1). Major bleeding appeared earlier in patients with an IVC filter than in those without filter (94% within the 1st month after the index VTE event, compared to 69% in those not receiving a filter; $p<0.001$). Intracranial bleeding was more common in patients receiving an IVC filter than in those who did not (17% vs. 11%; odds ratio [OR]: 1.70; 95% CI 1.02–2.83). There were no further differences in other variables (bleeding site, initial VTE presentation, risk factors for VTE or underlying conditions at baseline).

Immediately after bleeding, anticoagulation was discontinued in all patients. Ninety-five (78%) patients who had

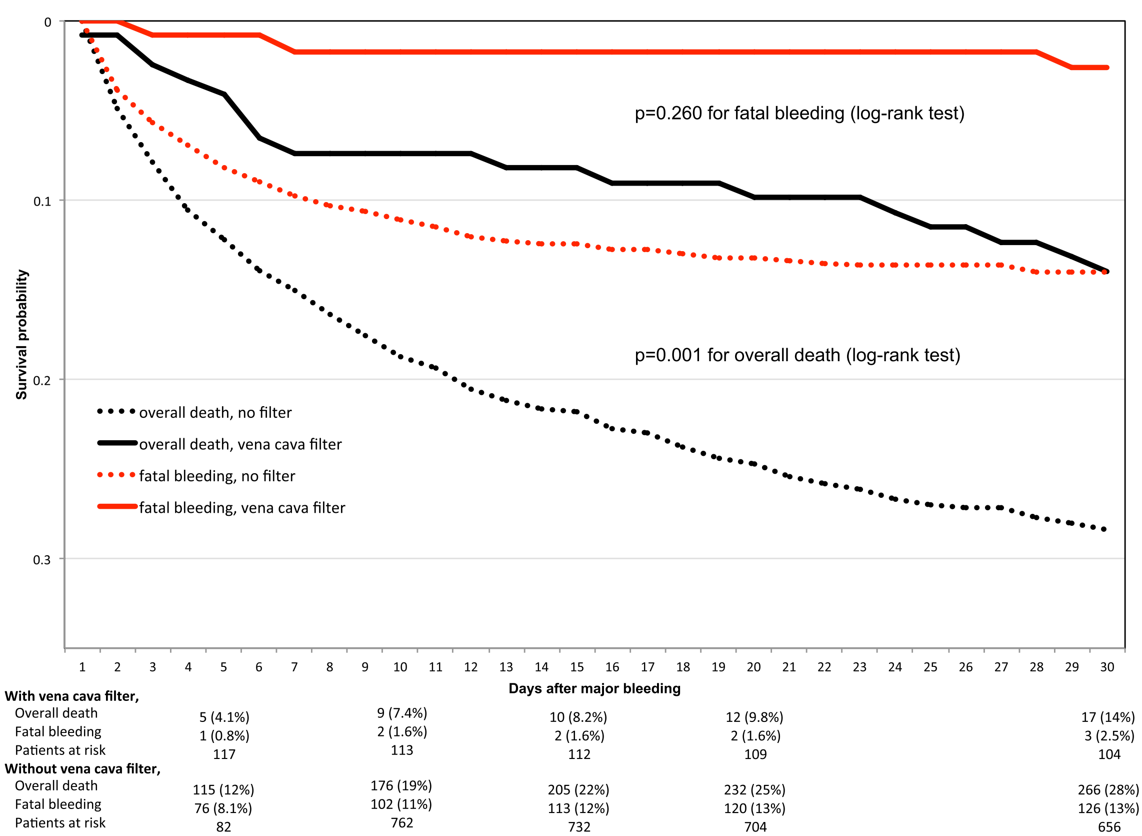

Fig. 2 Cumulative mortality (Kaplan–Meier curves) within the first 30 days after major bleeding, according to insertion of vena cava filter

a filter and 606 (64%) who did not have an IVC filter were restarted on anticoagulant therapy (Table 2). Anticoagulant therapy was restarted later in patients receiving an IVC filter than in those without filter: 48 h after major bleeding, 23% of patients with filter and 34% without filter ($p = 0.017$) had restarted anticoagulation. Among patients restarting therapy with low-molecular-weight heparin (LMWH), mean daily doses were lower in patients with an IVC filter than in those without filter (95 ± 52 vs. 104 ± 55 IU/kg/day LMWH, respectively; $p = 0.001$). Among patients who received an IVC filter, those who subsequently died had restarted anticoagulation non-significantly earlier than those who survived (median, 1.5 vs. 4 days after bleeding; $p = 0.28$). Among patients not receiving a filter, those who died had restarted anticoagulation significantly earlier than those who survived (median, 1 vs. 3 days; $p = 0.001$).

During the first 30 days after bleeding, 283 of 1065 patients died (27%; 95% CI 24–29%), 63 suffered major re-bleeding (5.9%; 95% CI 4.6%–7.5%), 19 had subsequent PE (1.8%; 95% CI 1.1%–2.7%) and 21 subsequent DVT (2.0%; 95% CI 1.3%–2.9%), as shown in Table 3. The most common cause of death was bleeding itself, accounting for 129 of 283 (46%) deaths, and most these deaths (77 of 129, 60%) occurred within the first 5 days after the bleeding event (Fig. 2). One in every two deaths in each group was unrelated to VTE or bleeding.

During the first 30 days after bleeding, patients receiving an IVC filter had a lower rate of all-cause death (HR 0.41; 95% CI 0.24–0.70) or fatal bleeding (HR 0.16; 95% CI 0.05–0.52), a similar rate of major re-bleeding (HR 0.65; 95% CI 0.26–1.66) or subsequent PE (HR 1.46; 95% CI 0.42–5.09) and a higher rate of DVT recurrences (HR 3.20; 95% CI 1.22–8.41) than those not receiving an IVC filter. Thirty-day mortality rate was highest in patients with intracranial (35%; 95% CI 27–43%), gastrointestinal (34%; 95% CI 29–28%) or genitourinary bleeding (33%; 95% CI 24–44%) and lowest in patients with hematoma (15%; 95% CI 11–20%). Fatal bleeding was the most likely cause of death in patients with intracranial (30 of 43 deaths, 70%) or retroperitoneal (12 of 17 deaths, 71%) bleeding. Fatal PE was more common after intracranial (4 of 43 deaths, 9.3%) or genitourinary (3 of 28 deaths, 11%) bleeding.

Results of the propensity score matching involved 559 patients who survived the first 24 h after major bleeding (122 with IVC filter and 429 without filter). The matched sample was well balanced in all variables (Table 4; Fig. 3). We performed a multivariable analysis including the following variables as covariates: patient's age, gender, existence of chronic lung disease, chronic heart disease, prior major bleeding, recent surgery, recent immobility, active cancer, metastases, unprovoked VTE (vs. provoked), anemia, abnormal platelet count, creatinine clearance levels, initial presentation of VTE (PE vs. DVT), time elapsed since VTE to major bleeding, intracranial bleeding (vs. other locations), hospital size and country of VTE diagnosis. During the first 30 days after bleeding, the matched analysis (with a ratio 4:1 and caliper of 0.1 of standard deviation) revealed a significantly lower risk for all-cause death (HR 0.49; 95% CI 0.31–0.77) and for fatal bleeding (HR 0.16; 95% CI 0.07–0.49), a non-significantly lower risk for non-fatal major re-bleeding (HR 0.55; 95% CI 0.23–1.40), a similar risk for PE recurrences (HR 1.57; 95% CI 0.38–6.36) and a non-significantly higher risk for DVT recurrences (HR 3.09; 95% CI 0.99–9.56) (Table 5).

To better explore the sensitivity of our findings, we repeated the analysis after excluding all those patients who died within the first 48 h (instead of 24 h). So, 46 additional patients that died on the 2nd day were also excluded. The matched analysis confirmed that patients undergoing an IVC filter were at a lower risk for all-cause death (HR 0.52; 95% CI 0.31–0.89) and for fatal bleeding (HR 0.16; 95% CI 0.04–0.64), a similar risk for PE recurrences (HR 0.79; 95% CI 0.21–2.94) and a higher risk for DVT recurrences (HR 3.33; 95% CI 1.02–10.9).

Discussion

Our data, obtained from a large series of VTE patients presenting with major bleeding during the first 3 months of anticoagulant therapy, confirm that their 30-day mortality rate was high (529 of 1314 patients, 40%). After excluding 246 patients who died within the first 24 h (to avoid immortal time bias) [11], there still remain 283 patients who died between Day 2 and Day 30. Of these, almost half (46%) died of bleeding. Our study revealed that patients receiving an IVC filter had half the mortality rate at 30 days than those not receiving a filter. Our initial hypothesis was that, with IVC filters in place, there would be a lower risk for subsequent PE if anticoagulation is withheld. However, the lower risk for all-cause death (and for fatal bleeding) found in our study was associated with a similar risk for PE recurrences and a non-significantly lower risk for major re-bleeding.

Our findings remained consistent after adjusting for potential confounders, and may at least in part be explained by the fact that patients receiving an IVC filter restarted anticoagulant therapy later and with lower doses of LMWH than those not receiving an IVC filter. The lack of difference on subsequent PEs—the principle outcome expected to be improved by insertion of an IVC filter—is likely reflective of counterbalancing effects from some protection by IVC filters versus less protection because of the delayed/ less potent anticoagulation in the IVC filters group, and more potent antithrombotic therapy in the no IVC filters group, which likely came at the cost of excess bleeding events [23–25]. Additional studies are required to better determine

Table 4 Clinical characteristics after matching of 551 patients with major bleeding during the first 3 months of anticoagulation, according to use of vena cava filter

	Vena cava filter	No vena cava filter	Odds ratio (95% CI)	*p*
Patients, n	122	429		
Hospital size > 500 beds	84 (69%)	276 (64%)	1.23 (0.80–1.89)	0.36
Country of origin,				
Spain	97 (80%)	352 (82%)	0.85 (0.51–1.41)	0.52
Clinical characteristics				
Male gender	51 (42%)	179 (42%)	1.00 (0.67–1.51)	0.99
Age (mean years ± SD)	69 ± 15	72 ± 15	–	0.06
Body weight (kg ± SD)	75 ± 16	72 ± 15	–	0.03
Initial VTE presentation				
Pulmonary embolism	76 (62%)	250 (58%)	1.18 (0.78–1.79)	0.43
Time from VTE to bleeding				
Mean days (± SD)	10 ± 13	13 ± 14	–	0.03
Day 0 to Day 30	115 (94%)	407 (94.9%)	0.89 (0.37–2.13)	0.79
Day 31 to Day 90	7 (5.7%)	22 (5.1%)	1.13 (0.47–2.70)	
Current therapy at bleeding				
Low-molecular-weight heparin	89 (73%)	286 (67%)	1.35 (0.86–2.11)	0.19
Unfractionated heparin	15 (12%)	34 (7.9%)	1.63 (0.86–3.10)	0.14
Thrombolytics	2 (1.6%)	11 (2.6%)	0.63 (0.14–2.90)	0.55
Fondaparinux	0	8 (1.9%)	–	0.13
Direct oral anticoagulants	0	3 (0.7%)	–	0.35
Vitamin K antagonists	11 (9.0%)	70 (16%)	0.51 (0.26–0.99)	0.045
Site of major bleeding				
Gastrointestinal	34 (28%)	129 (30%)	0.90 (0.58–1.40)	0.64
Haematoma	27 (22%)	127 (30%)	0.68 (0.42–1.09)	0.11
Intracranial	21 (17%)	54 (13%)	1.44 (0.83–2.50)	0.19
Retroperitoneal	15 (12%)	33 (7.7%)	1.68 (0.88–3.21)	0.11
Genitourinary	6 (4.9%)	37 (8.6%)	0.55 (0.23–1.33)	0.18
Other	19 (16%)	49 (11%)	1.43 (0.81–2.54)	0.22
Risk factors for VTE				
Surgery	21 (17%)	66 (15%)	1.14 (0.67–1.96)	0.63
Immobility ≥ 4 days	44 (36%)	157 (37%)	0.98 (0.64–1.49)	0.91
Active cancer	34 (28%)	119 (28%)	1.01 (0.64–1.58)	0.98
Estrogen use	5 (4.1%)	10 (2.3%)	1.79 (0.60–5.34)	0.29
Pregnancy/puerperium	0	1 (0.7%)	–	0.35
None of the above (unprovoked)	45 (37%)	142 (33%)	1.18 (0.78–1.80)	0.44
Prior VTE	9 (7.4%)	54 (13%)	0.55 (0.27–1.16)	0.11
Underlying conditions				
Chronic lung disease	19 (16%)	71 (17%)	0.93 (0.54–1.62)	0.80
Chronic heart failure	12 (9.8%)	53 (12%)	0.77 (0.40–1.50)	0.45
Anemia	67 (55%)	247 (58%)	0.90 (0.60–1.35)	0.60
CrCl levels < 30 mL/min	14 (12%)	63 (15%)	0.75 (0.41–1.40)	0.37

VTE venous thromboembolism, *SD* standard deviation, *LMWH* low-molecular-weight heparin, *CrCl* creatinine clearance, *CI* confidence intervals

the optimal timing and intensity for re-initiation of anticoagulation in such patients.

The present study has a number of potential limitations. First, data from registries are susceptible to selection bias if a non-representative sample of patients is selected for analysis. However, the RIETE registry captures a broad range of consecutive patients with symptomatic VTE from multiple medical centers, countries, and treatment settings, making it less likely that the study cohort is made up of a skewed population. Second, residual confounding is a likely

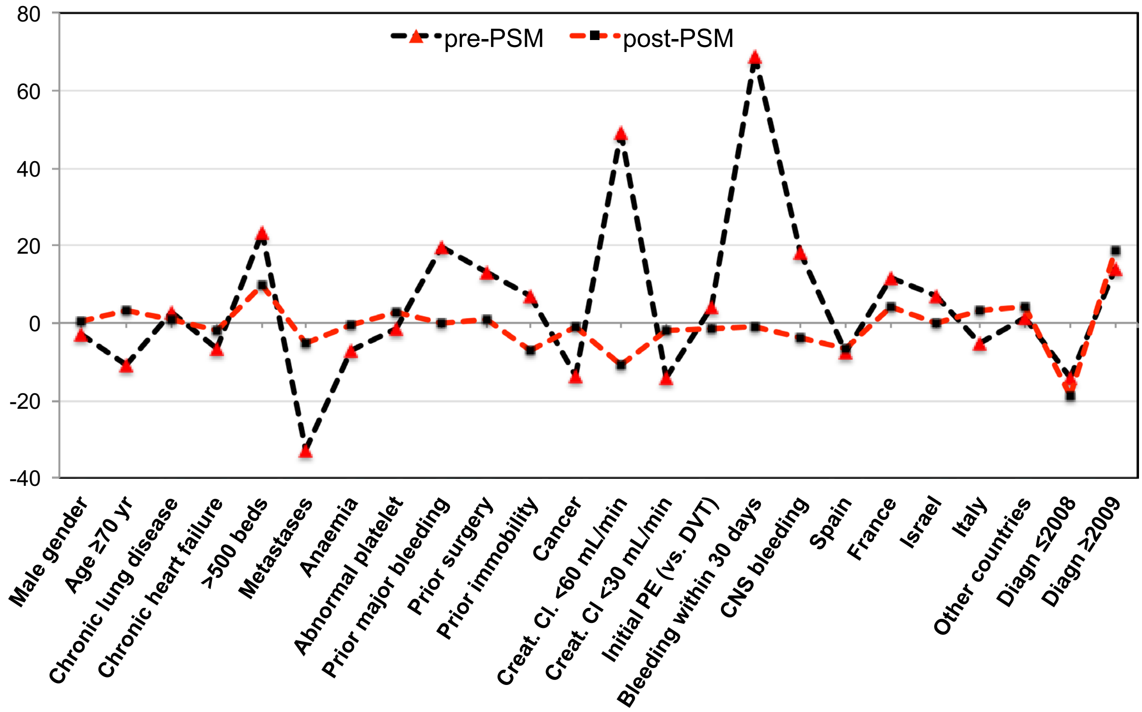

Fig. 3 Standardized differences of means of covariates before and after propensity score matching

Table 5 Uni- and multivariable analyses of the risk to develop VTE recurrences, major bleeding or death before and after PSM matching

	Before matching (univariate analysis)		Multivariable analysis after matching, with a ratio 4:1	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Patients, *n*	122 vs. 943		122 vs. 429	
Recurrent PE	1.31 (0.38–4.49)	0.67	1.57 (0.38–6.36)	0.52
Recurrent DVT	2.78 (1.08–7.18)	0.03	3.09 (0.99–9.56)	0.051
Re-bleeding	0.61 (0.24–1.51)	0.28	0.55 (0.23–1.40)	0.21
Overall death	0.45 (0.28–0.74)	0.002	0.49 (0.31–0.77)	0.003
Fatal bleeding	0.17 (0.06–0.54)	0.003	0.16 (0.07–0.49)	0.002

Fatal PE does not appear in the table since the event rate was too low to allow convergence of the model

PE pulmonary embolism, *DVT* deep vein thrombosis, *CI* confidence intervals

concern (either as for indication for IVC filter use, or as a measure of quality of care) and patients may have had systematic differences in unmeasured factors. However, we did have access to and adjusted for many important clinical variables and for hospital factors in the PSM models. Even if some residual confounding exists, it is unlikely that such confounding factors account for the entire effect size that we observed. Third, we studied only the initial 30-day period after bleeding. Fourth, it is not entirely clear that the delay in reinitiating anticoagulant therapy and/or lowering its doses was exclusively due to the presence of an IVC filter. Moreover, simply lowering doses and delaying initiation of therapy could portend a survival benefit, independent of IVC filter placement. These issues may confound the results of this analysis. Fifth, even in our large registry, numbers are small, and therefore, the robustness of their findings may be questioned. Finally, our data are hypothesis generating and must be validated by properly designed trials. Although these concerns are valid, our data probably represent the largest available pool of prospectively collected information in this patient population. It is extremely unlikely that a randomized trial be ever conducted in this setting. Although facing some limitations, our data could inform practice, until larger high-quality data emerge.

In conclusion, our study showed that in VTE patients experiencing major bleeding during the first 3 months of anticoagulant therapy, mortality rates, including fatal bleeding are common. Use of an IVC filter was associated with reduced rates of fatal bleeding and all-cause mortality. Fatal bleeding is a major driver of mortality in these patients and future efforts should help identify safer strategies (including timing, drug, and dose) for re-initiation of anticoagulation in VTE patients who suffer from major bleeding.

Acknowledgements We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for a 24.35% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support.

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Funding The sponsors of the study (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Compliance with ethical standards

Conflict of interest Dr. Bikdeli is supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, through grant number T32 HL007854. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Bikdeli reports that he was approached by lawyers on behalf of plaintiffs in litigation related to IVC filters. He was contacted as a result of a Viewpoint published elsewhere in the past. The lawyers were unaware of the current submission and this manuscript has not been shared with them. The current study was designed before the communication related to the litigation case. Dr. Moustafa has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi; and has received grants from Sanofi, Bayer HealthCare and LFB. Dr. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer, and Sanofi; has served as a speaker or a member of a speaker's bureau for Bayer HealthCare Pharmaceuticals, Daiichi-Sankyo, Leo Pharma, and Sanofi; and has received grants for clinical research from Sanofi and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the author.

Informed consent Informed consent was obtained from all individual participants included in the study.

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